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(54) **Cross-linked hydroxyethyl starch**

(57) Cross-linked hydroxyethyl starch is proposed as a new substance per se. Its use as an absorbent for wound secretions is found to accelerate healing. A method of making such starch comprises cross-linking hydroxyethyl starch with the aid of a cross-linking reagent, preferably under sterile conditions.

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SPECIFICATION

Cross-linked hydroxyethyl starch

The hospital stay of a patient is often considerably prolonged by protracted interference with the healing of wounds because the invasive growth of micro-organisms on the culture medium of the wound secretion nullifies the healing tendency. Particularly affected by interference in the healing of wounds are patients having second and third degree burns with chronically infected wounds, with ulcus cruras or decubitus as well as in the case of diabetic gangrene. Extensive and prolonged tissue necroses often develop which prolong healing of the patient by weeks and months. Hitherto, therapy aimed to cleanse the wound, remove inflammation and oedema and enhance granulation and involved considerable expense on drugs and extensive manipulation, often associated with considerable pain for the patient.

The invention is based on the problem of providing a new substance which can also be employed as an absorbent for wound secretion.

Surprisingly, it has been found that cross-linked hydroxyethyl starch solves the underlying problem of the invention.

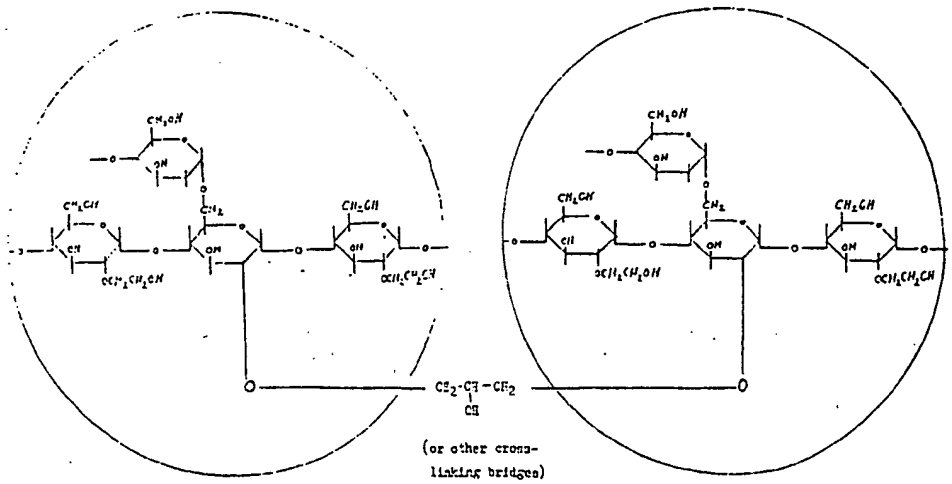
The advantages that can be achieved by means of the invention reside in the fact that the solubility in water of the hydroxyethyl starch modified by the cross-linking is markedly reduced so that, by reason of its gel character, it can absorb large quantities of secretions from wounds. The effect is accounted for by the fact that the gel-like cross-linking product can receive liquid in its cavities and thereby swell.

The cross-linking will be explained with reference to an example:

Hydroxyethyl starch + (= HES)	Cross-linking agent (e.g. epichlorhydrin)	Three-dimensional network

or, expressed as a chemical formula:

The hydroxyethyl starches employed for cross-linking preferably comprise a proportion of at least 90% amylopectin hydrolysate, an inherent viscosity of 0.05 - 0.30 dl/g at 25°C, an ether substituion coefficient of 0.00 - 0.90 hydroxyethyl groups per starch molecule, a weight averaged molecular weight $\overline{M}_w$ of 20,000 to 3 million and a particle-averaged molecular weight $\overline{M}_n$ of 10,000 to 1 million as well as an ethyleneglycol proportion of less than 0.5%. The strongly branched amylopectin structure is the basis for the various products possible according to molecular weight, substitution coefficient or type of cross-linking.



Cross-linking can also be achieved with cross-linking agents other than epichlorhydrin, e.g. oxalylchoride, methylenediisocyanate, formaldehyde, succinimide, halogen-acetic acid derivative, dicarboxylic acid chloride, metaphosphate, phosphoroxy chloride or the like.

The method of the invention for making cross-linked hydroxy-ethyl starch will be described with reference to the following example:

5 g HES 200/0.5 are dissolved in 100 ml 0.1 N soda lye. With stirring, 1 to 5 ml epichlorhydrin are then added depending on the desired degree of cross-linking. The reaction mixture is then left to stand at room temperature until a gel has formed. The product is neutralized with diluted hydrochloric acid, washed or reprecipitated with acetone and dried for 3 hours at 60°C. The absorption of water by the gel that has formed (ml water per gram of dry substance) is ascertained in known manner.

The swellability of the substance according to the invention can be varied at will by selecting the molecular weight, hydroxyethylisation coefficient, length of reticular chain, density of the cellular structure and the nature of the linkage. When employing cross-linked hydroxyethyl starch as a sterile dusting powder, it is possible to achieve considerable simplification in tending to a wound and cleansing it. Healing of the wound is accelerated by the repeated protective absorption of secretion without the need for touching the wound. The function as an absorbent for wound secretions can be explained as follows:

a) The wound is intensively dusted with cross-linked hydroxyethyl starch and covered with a light bandage.

b) Within a few hours, the cross-linked hydroxyethyl starch absorbs the secretion which is contaminated with micro-organisms (bacteria, viruses, fungi) and produces a continuous flow of secretion of the wound. Oedema and inflammation mediators are absorbed, the wound remains moist and elastic and no clotting takes place.

c) After the cross-linked hydroxyethyl starch is laden with wound secretion, it is rinsed off with water and new cross-linked hydroxyethyl starch is applied, usually once per day.

d) After about two weeks of treatment, infections, erythemae and oedema have disappeared from the wound and fresh granulation tissue has formed.

To facilitate the function as an absorbent for wound secretions, it is advantageous to carry out production and further treatment of the cross-linked hydroxyethyl starch under sterile conditions. It is also possible to use the cross-linked hydroxyethyl starch in conjunction with a bacteriostatic agent, e.g. silver sulphadiazine.

CLAIMS

1. Cross-linked hydroxyethyl starch.
2. Hydroxyethyl starch according to claim 1, characterised in that the hydroxyethyl starch comprises a proportion of at least 90% amylopectin.
3. Hydroxyethyl starches according to claim 1 or claim 2, characterised in that the hydroxyethyl starch has an ether substitution coefficient of up to 0.90 hydroxyethyl groups per starch molecule.
4. Cross-linked hydroxyethyl starch according to one of claims 1 to 3, characterised in that the ethyleneglycol proportion of the hydroxyethyl starch is less than 0.5 parts by weight of ethyleneglycol per 100 parts of modified starch.
5. Hydroxyethyl starch according to one of claims 1 to 4, characterised in that the cross-linking of the hydroxyethyl starch is effected by way of glycerine or other bifunctional radicals.
6. A method of making cross-linking hydroxyethyl starch according to one of claims 1 to 5, characterised in that the hydroxyethyl starch is cross-linked with the aid of a cross-linking reagent.
7. A method according to claim 6, characterised in that the cross-linking reagent is epichlorohydrin, diisocyanate, succinimide, halogen-acetic acid derivative, dicarboxylic acid chloride, formaldehyde, metaphosphate, phosphoroxy chloride or the like.
8. A method according to claim 6 or claim 7, characterised in that the production of cross-linked hydroxyethyl starch takes place under sterile conditions.
9. The use of cross-linked hydroxyethyl starch according to any one of claims 1 to 8 as a wound secretion absorbent.

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